CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040148

Trade Name : HYDROCODONE AND ACETAMINOPHEN TABLETS USP

Generic Name: Hydrocodone and Acetaminophen Tablets USP 10mg/325mg and 10mg/500mg

Sponsor : WATSON LABORATORIES, INC.

Approval Date: FEBRUARY 14, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040148

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040148

APPROVAL LETTER

ANDA 40-148

FEB 14 1997

Watson Laboratories, Inc.
Attention: David C. Hsia, Ph.D.
311 Bonnie Circle
Corona, CA 91720

Dear Dr. Hsia:

This is in reference to your abbreviated new drug application dated June 7, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/325 mg (Norco™) and 10 mg/500 mg.

Reference is also made to your amendments dated October 2, November 5, and December 9, 1996.

We have completed the review of this abbreviated application and have concluded that these drugs are safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The drug product, Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/325 mg (Norco™) can be expected to have the same therapeutic effect as that of the listed drug product upon which the Agency relied as the basis of safety and effectiveness. The Division of Bioequivalence has determined your, Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/500 mg, to be bioequivalent and, therefore, therapeutically equivalent to that of the listed drug (Lortab® 10/500 Tablets, of D.M. Graham Laboratories, Inc.). Your dissolution testing should be incorporated into the stability and quality control programs using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of these drugs.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

D. L. Spoon 2/14/97

Douglas L. Spoon
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040148

CHEMISTRY REVIEW

Office of Generic Drugs
Division of Chemistry II

ANDA Review

1. CHEMIST'S REVIEW NO.: 4

2. ANDA #: 40-148

3. NAME AND ADDRESS OF APPLICANT

Watson Laboratories
Attention: David C. Hsia, Ph.D.
311 Bonnie Circle
Corona, CA 91720

4. LEGAL BASIS FOR SUBMISSION

Reference Drug: D. M. Graham Laboratories, Inc.; Lortab® 10/500
Strength: 5 mg/500 mg (see orange book 16th edition, supplement 8).

Reference Drug: Vicodin/Knoll Pharmaceuticals, Inc.
Strength: 5 mg/500 mg
Also petition of Mikart for 10 mg/325 mg strength approved on 6.8.87

Rating: AA (page 32)
No patents or exclusivity remaining.

Revised patent certification letter included.

5. SUPPLEMENTS: None

6. PROPRIETARY NAME: None

7. NONPROPRIETARY NAME: Hydrocodone Bitartrate and Acetaminophen Tablets USP

8. SUPPLEMENT PROVIDE FOR: None

9. AMENDMENTS AND OTHER DATES:

Firm:

06.07.95: Original Submission
07.26.95: Amendment
04.02.96: Amendment
10.02.96 - Amendment
11.5.96: Amendment (Labeling)
12.09.96 - Amendment **Subject of this review**

FDA

07.10.95: Acceptable for filing
02.16.96: NA letter#1
09.13.96: NA letter #2

10. PHARMACOLOGICAL CATEGORY: Analgesic for moderate to severe pain.

11. HOW DISPENSED: R_x

12. RELATED IND/NDA/DMF(s):

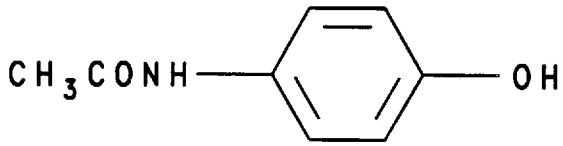
13. DOSAGE FORM: Tablets

14. POTENCIES: 10 mg/325 mg and 10 mg/500 mg

15. CHEMICAL NAME AND STRUCTURE:

Acetaminophen USP

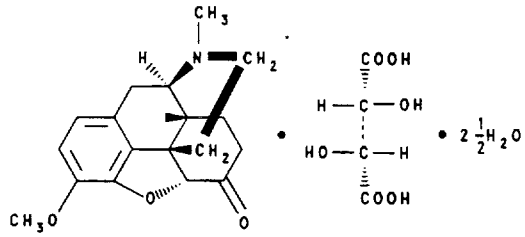
$C_8H_9NO_2$; M.W. = 151.16



4'-Hydroxyacetanilide. CAS [103-90-2]

Hydrocodone Bitartrate USP

$C_{18}H_{21}NO_3.C_4H_6O_6.2\frac{1}{2}H_2O$; M.W = 494.50



4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1)

hydrate (2:5). CAS [34195-34-1; 6190-38-1]

16. RECORDS AND REPORTS: None

17. COMMENTS:
    a. The manufacturing process record is satisfactory.
    b. Professional Labeling review - satisfactory, C. Hoppes, 11.8.96.
    c. EER acceptable, 11.30.95; up date requested 11.29.96
    d. Bio-review - acceptable, J. Lee, 11.20.95
    e. MV not required, compendial articles; tests, methods and specifications per compendial monographs.

18. CONCLUSIONS AND RECOMMENDATIONS : The application submission as amended is satisfactory in CMC and labeling and is APPROVED.

19. REVIEWER: U. V. Venkataram, Ph.D. DATE OF REVIEW: 01-13-97

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040148

FINAL PRINTED LABELING

NDC 52544-539-01

NORCO™
hydrocodone* bitartrate
and acetaminophen
tablets, USP

C III

10 mg/325 mg

EACH TABLET CONTAINS:
Hydrocodone* Bitartrate, USP....10 mg
*(WARNING: May be habit forming)
Acetaminophen, USP.....325 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Dispense in a tight, light-resistant container with a child-resistant closure.

USUAL ADULT DOSAGE:
One tablet every four to six hours, as needed for pain.

Total daily dosage should not exceed six tablets.

See insert for full prescribing information.

Keep this and all medication out of the reach of children.

Store at controlled room temperature 15°-30°C (59°-86°F).

Watson Laboratories, Inc. Corona, CA 91720

13058

3 52544-539-01 1

LOT NO.:
EXP:

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals Inc

WATSON LABORATORIES, INC.

NDC 52544-540-01

HYDROCODONE BITARTRATE and ACETAMINOPHEN TABLETS, USP
10 mg/500 mg

C III

Each Tablet Contains:
Hydrocodone Bitartrate, USP.....10 mg
(Warning: May be habit forming)
Acetaminophen, USP.....500 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

Dispense in a tight, light-resistant container with a child-resistant closure.

Usual Adult Dosage: One tablet every four to six hours, as needed for pain. Total daily dosage should not exceed six tablets.

See insert for full prescribing information.

Keep this and all medication out of the reach of children.

Store at controlled room temperature 15°-30°C (59°-86°F)

Watson Laboratories, Inc.
Corona, CA 91720

Lot No.:
Exp:

NDC 525

N(

hydroc
and acetaminophen
tablets, USP

10 mg/325 mg

EACH TABLET CONTAINS:
Hydrocodone* Bitartrate, USP....10 mg
*(WARNING: May be habit forming)
Acetaminop

CAUTION: F
dispensing

Dispense in a tight, light-resistant container with a child-resistant closure.

USUAL ADULT DOSAGE:
One tablet every four to six hours, as needed for pain.

Total daily dosage should not exceed six tablets.

3 52544-539-05

WATSON Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals Inc

NDC 52544-540-05

HYDROCODONE BITARTRATE and ACETAMINOPHEN TABLETS, USP
10 mg/500 mg

C III

Each Tablet Contains:
Hydrocodone Bitartrate, USP.....10 mg
(Warning: May be habit forming)
Acetaminophen, USP.....500 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

WATSON LABORATORIES, INC.

Dispense in a tight, light-resistant container with a child-resistant closure.

Usual Adult Dosage: One tablet every four to six hours, as needed for pain.

Total daily dosage should not exceed six tablets.

See insert for full prescribing information.

Keep this and all medication out of the reach of children.

Store at controlled room temperature 15°-30°C (59°-86°F)

Watson Laboratories, Inc.
Corona, CA 91720

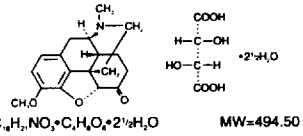
Lot No.:
Exp:

NORCO™ TABLETS C III

DESCRIPTION

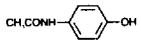
NORCO™ (Hydrocodone bitartrate and acetaminophen) is supplied in tablet form for oral administration.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$ MW=494.50

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_8H_9NO_2$ MW=151.16

Each NORCO™ tablet contains:

Hydrocodone Bitartrate **(WARNING:** May be habit forming)	10 mg
Acetaminophen	325 mg

In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, crospovidone, D&C yellow #10 aluminum lake, magnesium stearate, microcrystalline cellulose, pregelatinized starch, povidone and stearic acid.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxymetabolites.

See **OVERDOSAGE** for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See **OVERDOSAGE** for toxicity information.

INDICATIONS AND USAGE

NORCO™ Tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

NORCO™ Tablets should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

General: Special Risk Patients: As with any narcotic analgesic agent, NORCO™ Tablets should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when NORCO™ Tablets are used postoperatively and in patients with pulmonary disease.

Information for Patients: NORCO™ Tablets, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: Patients receiving narcotics, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with NORCO™ Tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:

Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. NORCO™ Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to deliver will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all narcotics, administration of NORCO™ Tablets to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NORCO™ Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of NORCO™ Tablets may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see **OVERDOSAGE**).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the **OVERDOSAGE** section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: NORCO™ Tablets are classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, NORCO™ Tablets should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when NORCO™ Tablets are used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks, of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.

HOW SUPPLIED

NORCO™ is supplied as a yellow, capsule-shaped tablet containing 10 mg hydrocodone bitartrate and 325 mg acetaminophen, bisected on one side and debossed with "NORCO 539" on the other side.

Bottles of 100	NDC 52544-539-01
Bottles of 500	NDC 52544-539-05

Store at controlled room temperature, 15° - 30°C (59°- 86°F).
Dispense in a tight, light-resistant container with a child-resistant closure.

Watson Laboratories
Corona, CA 91720

Revised September 11, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040148

BIOEQUIVALENCE AND DISSOLUTION REVIEWS

ANDA 40-148

Watson Laboratories
Attention: David C. Hsia, Ph.D.
311 Bonnie Circle
Corona CA 91720

NOV 20 1995

Dear Sir:

Reference is made to your abbreviated new drug application dated June 7, 1995, submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/325 mg and 10 mg/500 mg.

The following comments pertain **only** to bioequivalency issues in the June 7, 1995 submission.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of pH 5.8 phosphate buffer at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

   Not less thar of the labeled amount of **both** components in the tablet is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

for

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

NOV 16 1995

Hydrocodone Bitartrate; Acetaminophen
10 mg/325 mg and 10 mg/500 mg tablet
NDA #40-148
Reviewer: J. Lee
40148DW.695

Watson Labs
Corona, Calif.
Submission date:
June 7, 1995

Review of Two Requests for Waiver

The sponsor has submitted an application for hydrocodone bitartrate; acetaminophen, 10 mg/325 mg and 10 mg/500 mg tablet and has requested a waiver of in-vivo bioavailability studies based on comparative dissolution profiles between the test products vs Vicodin® (Knoll Pharmaceutical) [appended].

The company seeks to market new strengths of the drug product allowed under citizen's petitions 87 P-0129/CP and 87 P-0170/CP. [see attachments]

Previously, the company had submitted applications for the same strengths of the test product under different application numbers. NDA #81-081 [HCB;APAP - 10;500 mg] was withdrawn July 28, 1994. NDA #81-078 [HCB;APAP - 10;325 mg] was withdrawn February 10, 1993.

The drug product is AA listed in the Therapeutic Equivalence List.

Comment:

1. The dissolution profiles for both strengths of the test drug product are acceptable. The dissolution profile for the acetaminophen component of the reference batch (#106760654) does not meet Q dissolved in 30 minutes). The mean of the 12 units tested and 4 individual units fail the specification.

2. The Divison of Scientific Investigations, Office of Compliance will be notified regarding the Knoll product not meeting dissolution specifications.

3. The batch size for both lots of the test product units.

Recommendation:

1. The dissolution testing conducted by Watson Labs on its hydrocodone bitartrate; acetaminophen, 10 mg/325 mg and 10 mg/500 mg, batch #R49994 and R49894, respectively, is acceptable.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of pH 5.8 phosphate

buffer at 37°C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

> Not less than of the labeled amount of both components in the tablet is dissolved in 30 minutes.

3. The Division of Bioequivalence finds that the information submitted by the sponsor demonstrates that the test products fall under 21 CFR 320.22 (c) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in-vivo bioavailability study be granted.

R. Lee 11/14/95

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK N. Patnaik 11/14/95

Concur: _____ Date: 11/16/95

Keith Chan, Ph.D.
Director, Division of Bioequivalence

JLee/jl/10-31-95

cc: NDA #40-148 (original, duplicate), HFD-630, HFD-600 (Hare), HFD-655 (Lee, Patnaik), HFC-130 (JAllen), Drug File, Division File

USP XXIII Apparatus II Basket____ Paddle x rpm 50

Medium: pH 5.8 phosphate buffer Volume: 900 ml

Number of Tabs/Caps Tested: 12

Reference Drug: Vicodin 5 mg hydrocodone; 500 mg acetaminophen

Assay Methodology: _____

HCB;APAP 10;325 mg

Results

Hydrocodone bitartrate

Time (min)	Test Product (10 mg) Lot # R49994 Mean % Dissolved	Range	(SD)	Reference Product (5 mg) Lot # 106760654 Mean % Dissolved	Range	(SD)
5	93.6		(5.5)	77.6		(13)
10	96.6		(2.6)	90.4		(9.5)
20	96.7		(1.7)	97.1		(4.4)
30	98.2		(1.6)	101.3		(3.6)
			( )			( )
			( )			( )
			( )			( )

Acetaminophen

	Lot # _____ (325 mg)			Lot # _____ (500 mg)		
5	96.1		(3.4)	51.9		(9.0)
10	97.7		(1.8)	66.6		(8.2)
20	98.8		(1.3)	74.5		(5.5)
30	99.3		(1.3)	78.4		(5.0)
			( )			( )
			( )			( )

USP XXIII Apparatus II Basket____ Paddle x rpm 50

Medium: pH 5.8 phosphate buffer Volume: 900 ml

Number of Tabs/Caps Tested: 12

Reference Drug: Vicodin 5 mg hydrocodone; 500 mg acetaminophen

Assay Methodology: _____

HCB;APAP 10;500 mg

Results

Hydrocodone bitartrate

Time (min)	Test Product (10 mg) Lot # R49894 Mean % Dissolved	Range	(SD)	Reference Product (5 mg) Lot # 106760654 Mean % Dissolved	Range	(SD)
5	91.7		(4.9)	77.6		(13)
10	95.4		(3.6)	90.4		(9.5)
20	97.1		(2.7)	97.1		(4.4)
30	97.5		(2.1)	101.3		(3.6)
			( )			( )
			( )			( )
			( )			( )

Acetaminophen

	Lot #_____ (500 mg)			Lot #_____ (500 mg)		
5	90.1		(2.1)	51.9		(9.0)
10	93.3		(2.5)	66.6		(8.2)
20	96.8		(2.7)	74.5		(5.5)
30	97.0		(2.3)	78.4		(5.0)
			( )			( )
			( )			( )

FEB 13 1997

Hydrocodone Bitartrate: Acetaminophen
10 mg/325 mg and 10 mg/500 mg tablet
NDA #40-148
Reviewer: J. Lee
40148DW.D96

Watson Labs
Corona, Calif.
Submission date:
December 9, 1996

Review of a Waiver Request (Amendment)

This application was previously reviewed (sub. date: June 7, 1995) by the Division of Bioequivalence and waivers were granted for the test products based on dissolution testing with Vicodin® (legal basis for submission). Subsequently, the D.M. Graham Laboratories product (Lortab®) became the reference listed product (1/26/96) for the 10 mg/500 mg strength tablet. The Division of Chemistry, therefore requested that the sponsor conduct dissolution testing between their 10 mg/500 mg test product vs the new RLD.

The drug product is AA listed.

Comment:

1. The dissolution testing is acceptable.

Recommendation:

1. The dissolution testing, using the USP XXIII method, conducted by Watson Labs on its hydrocodone bitartrate; acetaminophen 10 mg/500 mg tablet, batch #R49894, is acceptable.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of pH 5.8 phosphate buffer at 37°C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

   Not less than of the labeled amount of both components of the drug in the tablet is dissolved in 30 minutes.

3. The Division of Bioequivalence finds that the information submitted by the sponsor demonstrates that the test product falls under 21 CFR 320.22 © of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in-vivo bioavailability study be granted. Watson's hydrocodone bitartrate; acetaminophen 10 mg/500 mg tablet is deemed bioequivalent to Lortab® 10/500 manufactured by D.M. Graham Laboratories.

E. Lee 2/12/97

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

JLee/jl/02-04-97

cc: NDA #40-148 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

USP XXIII Apparatus II Basket _____ Paddle X rpm 50

Medium: pH 5.8 phosphate buffer Volume: 900 ml

Number of Tabs/Caps Tested: 12

Reference Drug: Lortab® 10/500 (D.M. Graham Laboratories)

Assay Methodology: _____

Results

Hydrocodone Bitartrate

Time (min)	Test Product Lot # R49894 Mean % Dissolved	Range	(CV)	Reference Product Lot # WL109674A Mean % Dissolved	Range	(CV)
5	97.1		(4.4)	99.5		(2.3)
10	98.2		(3.1)	99.2		(1.7)
20	98.2		(1.8)	98.1		(2.3)
30	100.1		(2.8)	98.7		(1.8)
			( )			( )
			( )			( )

Acetaminophen

	Lot # _____			Lot # _____		
5	94.6		(3.4)	97.7		(0.8)
10	95.5		(3.0)	98.8		(0.8)
20	96.6		(2.1)	98.7		(0.9)
30	97.4		(1.8)	98.4		(1.2)
			( )			( )
			( )			( )

DIV

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 40-148 SPONSOR: Watson Labs
DRUG: Hydrocodone bitartrate ; acetaminophen
DOSAGE FORM: tablet
STRENGTHS/(s): 10 mg /325 mg + 10 mg /500 mg
TYPE OF STUDY: Single_ Multiple___ Fasting_ Fed_ N/A
STUDY SITE:
N/A

~~STUDY SUMMARY:~~ NEW RLD for the 10 mg /500 mg (D.M. Graham) - Lortab - waiver granted based on 21 CFR 320.22 (c)
Previously, waivers for this application were based on ~~the~~ Vicodin® (Knoll) being the RLD.

Drug product AA listed

DISSOLUTION: USP method
OK

PRIMARY REVIEWER: Jenny Lee BRANCH: II

INITIAL: J.L. DATE 2/12/97

TEAM LEADER: S. Nerurkar, Ph.D BRANCH: II

INITIAL: [signature] DATE 2/13/1997

DIRECTOR, DIVISION OF BIOEQUIVALENCE: ~~Keith Chan, Ph.D~~
Acting Rabi Patnaik

INITIAL: [signature] DATE 2/13/97

DIRECTOR, OFFICE OF GENERIC DRUGS:

INITIAL:_____ DATE_____